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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,763	09/03/2003	Nicholas P. Barker	50206/014002	6915
21559	7590	12/05/2006	EXAMINER	
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			HISSONG, BRUCE D	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 12/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/654,763

Applicant(s)

BARKER ET AL.

Examiner

Bruce D. Hissong, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 September 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8, 10-19 and 21-25 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8, 10-19 and 21-25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/22/06</u> | 6) <input type="checkbox"/> Other: _____  |

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## DETAILED ACTION

### **Formal Matters**

1. Applicants' response to the office action mailed on 3/22/2006, including amendments to the specification and claims, and arguments/remarks, was received on 9/22/2006 and has been entered in to the record.

2. The Applicants cancelled claims 9 and 20, and added new claims 24 and 25 in the amendment received on 9/22/2006. Accordingly, claims 1-8, 10-19, and 21-25 are pending and are the subject of this office action.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 3/22/2006.

### **Information Disclosure Statement**

The information disclosure statement received on 9/22/2006 has been fully considered by the Examiner.

### **Specification**

Objection to the specification for improper use of trademarks, as set forth on page 2 of the office action mailed on 3/22/2006, is withdrawn in response to Applicants' amendments to the specification to properly identify trademarks.

### **Claim Rejections - 35 USC § 112, second paragraph**

#### **Rejections withdrawn**

1. Rejection of claims 1-8, 10-19, and 21-23 under 35 USC § 112, second paragraph, for being indefinite regarding the metes and bounds of asialo-interferons, as set forth on pages

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2-3 of the office action mailed on 3/22/2006, is withdrawn in response to Applicants' arguments that the instant specification adequately defines the term "asialo-interferon" on page 5, lines 5-23.

Rejection necessitated by amendment

2. Claims 1-8, 10-19, and 21-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claims 1, 11, and 21 recite a method of treating a patient comprising administration of (i) an effective amount of an asialo-IFN, and (ii) a second anti-neoplastic therapy. As written, the claims read on administration of a type of therapy. It is not clear how one of ordinary skill in the art could administer a type of therapy, and thus the claims are indefinite. For the purpose of examination, the Examiner has interpreted the claims as reading on administration of a second anti-neoplastic therapeutic agent, rather than administration of a therapy.

Claim Rejections - 35 USC § 103

1. Claims 1-8, 10-13, 15-19, and 21-23 remain rejected under 35 USC § 103(a) as being unpatentable over the combination of Takahashi, in view of Trere *et al* ("Trere"), and further in view of Treiber, as set forth on pages 3-4 of the office action mailed on 3/22/2006. In addition, new claims 24-25 are also rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Takahashi, Trere, and Treiber.

The amended claims of the instant invention are drawn to a method of treating a patient having liver cancer, wherein said method comprises administering a mammalian asialo-interferon and a second anti-neoplastic therapy. The claims are further drawn to said method of treating a patient having liver cancer, wherein said method further comprises a step to test said liver cancer for expression of an asialo-glycoprotein receptor. Takahashi teaches administration of asialo-interferons (IFN), including asialo-IFN- $\alpha$ , - $\beta$ , and - $\gamma$ , for treatment of liver disease, but does not teach a method of testing liver tissue for expression of asialo-glycoprotein receptors, and is also silent regarding administration of a second anti-neoplastic therapy. Treiber teaches several types of therapy for treatment of hepatocellular carcinoma, including surgical procedures, chemotherapy, radionuclide therapy, and IFN therapy, and also teaches IFN

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therapy combined with various chemotherapeutic agents. Trere discloses that asialo-glycoprotein receptors are overexpressed on human hepatocellular carcinoma cells compared to healthy liver cells, and teaches a liver biopsy-based method for determining the presences of asialo-glycoprotein receptors on liver cells.

In the response received on 9/22/2006, the Applicants argue that claims of the instant invention are not obvious in view of the combination of Takahashi, Trere, and Treiber because as currently amended, the claims read on a method of treating liver disease by administration of an asialo-IFN and a second anti-neoplastic therapy, and neither Takahashi, Trere, or Treiber teach or suggest co-administration of an asialo-IFN and a second anti-neoplastic therapy.

This argument has been fully considered and is not found persuasive. Treiber, on pages 313, 2<sup>nd</sup> column – 314, 1<sup>st</sup> column, explicitly teaches co-administration of IFN- $\alpha$  and various chemotherapeutic agents. In particular, on page 314, Treiber discusses results from a study in which patients with hepatocellular carcinoma were treated with cisplatin with and without IFN- $\alpha$ . Patients receiving combined cisplatin and IFN- $\alpha$  therapy responded more favorably than patients receiving only cisplatin alone. Thus, a skilled artisan would be motivated by the teachings of Treiber to treat patients with liver disease, such as hepatocellular carcinoma, with IFN therapy combined with an additional therapeutic agent, such as cisplatin. The teachings of Takahashi, which discloses administration of asialo-IFN for treatment of liver disease, would provide the motivation to administer asialo-IFNs, while, Trere, by teaching overexpression of asialo-glycoprotein receptors on hepatocellular carcinoma cells and a method of determining expression of said asialo-glycoprotein receptors, would provide motivation to determine expression of asialo-glycoprotein receptors on liver tissue prior to administration of asialo-IFNs. Furthermore, even if Treiber did not specifically disclose the results of studies in which liver disease was treated by co-administration of IFN and additional therapeutic agents, one of ordinary skill in the art would still be motivated by Treiber to combine IFN therapy with an additional anti-neoplastic therapy. Treiber discloses that IFN therapy alone was effective in treating hepatocellular carcinoma (p. 312, 1<sup>st</sup> column; see also p. 313), and also teaches other modes of treatment (e.g. chemotherapy, hormone therapy, radiation/radionuclide therapy - see Tables 1 and 2, and p. 312-313, 314-321). Thus, it would have been obvious to a person of ordinary skill in the art, at the time the invention was conceived, to co-administer IFNs and additional anti-neoplastic agents because these therapies are taught individually to be effective

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for treating liver disease such as hepatocellular carcinoma. *In re Kerkhoven* (205 USPQ 1069, CCPA 1980) summarizes:

*"It is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for the same purpose in order to form a combination that is to be used for the very same purpose: the idea of combining them flows logically from their having been individually taught in the prior art."*

Therefore, because Treiber provides motivation for combining IFN therapy with additional anti-neoplastic therapies, Takahashi teaches treatment of liver disease asialo-IFNs, and further teaches that asialo-IFNs are more effective than native IFNs and are less toxic, and Trere teaches that asialo-glycoprotein receptors are overexpressed on hepatocellular carcinoma cells and also teaches a method of determining expression of said receptors, the combined teachings of Takahashi, Treiber, and Trere would provide the skilled artisan with both the motivation, and a reasonable expectation of success, in practicing the invention set forth in claims 1-8, 10-13, 15-19, and 21-23 of the instant application.

2. Claim 14 remains rejected under 35 USC § 103(a) as being unpatentable over the combination of Takahashi in view of Kudo *et al* ("Kudo"), and further in view of Treiber, as set forth on page 5 of the office action mailed on 3/22/2006. The subject matter of the claims of the instant invention, as well as the teachings of Takahashi and Treiber, is discussed *supra*. Amended claim 14 is drawn to the method of claim 11, wherein the testing step to determine asialo-glycoprotein receptor expression comprises non-invasive imaging of the liver of said patient.

In the response received on 9/22/2006, the Applicants argue that claim 14, as currently amended, reads on a method of treating a patient with liver disease comprising administration of asialo-IFN and a second anti-neoplastic therapy, and the combination of Takahashi and Treiber do not teach or suggest such combined therapy. The Applicants further argue that Kudo also does not teach or suggest a method of administering asialo-IFN and a second anti-neoplastic agent, and therefore claim 14 cannot be obvious in view of the teachings of Takahashi, Treiber, and Kudo.

These arguments have been fully considered and are not found persuasive. As stated *supra*, the combined teachings of Treiber and Takahashi provide a skilled artisan with the

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motivation to co-administer asialo-IFN with a second anti-neoplastic agent. Kudo teaches a method of *in vivo*, non-invasive determination of asialo-glycoprotein expression. Thus, a skilled artisan would know of methods of treating liver disease by administration of asialo-IFNs (via Takahashi) or co-administration of IFNs and other anti-neoplastic agents (via Treiber), and a non-invasive method of determining asialo-glycoprotein receptor expression (via Kudo). Therefore, the combined teachings of Takahashi, Treiber, and Kudo would provide the skilled artisan with both the motivation, and a reasonable expectation of success, in practicing the invention set forth in claim 14 of the instant application.

### **Conclusion**

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH  
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**ROBERT S. LANDSMAN, PH.D**  
**PRIMARY EXAMINER**